CENTER FOR DRUG EVALUATION AND RESEARCH

75-217

APPLICATION NUMBER:

BIOEQUIVALENCE

1.1

Ibuprofen Oral Suspension Drops
40 mg/mL (or 50 mg/1.25 mL)
ANDA #75-217
Reviewer: Hoainhon Nguyen
WP #75217sd.997

L. Perrigo Company
Allegan, MI
Submission Date:
September 30, 1997

Review of Two Bioequivalence Studies and Dissolution Data

I. Background:

Ibuprofen is a member of the propionic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs) which possess anti-inflammatory, analgesic and antipyretic activity. Ibuprofen is indicated, in children, for the reduction of fever, relief of mild to moderate pain, and relief of signs and symptoms of juvenile arthritis, and, in adults, for relief of mild to moderate pain, treatment of primary dysmenorrhea, and relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis. The mode of action of Ibuprofen may be related to prostaglandin synthetase inhibition. Ibuprofen is a racemic mixture of [+]S and [-]R-enantiomers, practically insoluble in water, with a pKa of 4.4. After absorption of the racemic Ibuprofen, the [-]R-enantiomer undergoes interconversion to the [+]S-form. The biological activities of Ibuprofen are associated with the [+]S-enantiomer.

About 60% pharmacologically inactive [-]R-isomer is slowly interconverted into the active [+]S species in adults. The [-]R-isomer serves as a circulating reservoir to maintain levels of active drug. *In vivo* studies indicate that Ibuprofen is well absorbed orally from the suspension, drops, caplet and chewable tablet formulations, with peak plasma levels usually occurring within 1 to 2 hours. There was found no interference with the absorption of Ibuprofen when given in conjunction with an antacid containing both aluminum hydroxide and magnesium hydroxide. When taken with food, the rate but not the extent of absorption is affected, with TMAX being delayed by approximately 30 to 60 minutes, and peak levels being reduced by approximately 30 to 50%.

Ibuprofen is highly protein bound (>99%). Protein binding is saturable and at

concentrations >20μg/mL binding is non-linear. Following oral administration, the majority of the dose was recovered in the urine within 24 hours as the hydroxy-(25%) and carboxypropyl-(37%) phenylpropionic acid metabolites. The percentages of free and conjugated Ibuprofen found in the urine were approximately 1% and 14%, respectively. Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of Ibuprofen is virtually complete 24 hours after the last dose. It has a biphasic plasma elimination time curve with a half-life of approximately 2 hours.

The most frequent adverse effects of Ibuprofen include nausea, epigastric pain, heartburn, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, dizziness, headache, nervousness, rash, pruritis, tinnitus, decreased appetite, edema, and fluid retention.

Ibuprofen is available commercially as oral suspension, 100 mg/5 mL, Oral Drops, 40 mg/mL, oral tablets, 200 mg, 400 mg, 600 mg and 800 mg, chewable tablets, 50 mg and 100 mg, and film-coated tablets, 100 mg, 200 mg, 300 mg, 400 mg, 600 mg and 800 mg. The RLD product for the Oral Drop is MOTRIN® Oral Drop, 40 mg/mL, manufactured by McNeil.

The firm has submitted the results of a fasting, single-dose bioequivalence study and a non-fasting, single-dose bioequivalence study comparing its Ibuprofen Oral Drop, 40 mg/mL, with McNeil's Motrin® Oral Drop, 40 mg/mL. Comparative dissolution data for the test and RLD products are also submitted.

II. Bioequivalence Studies:

A. Fasting Study: (Protocol No. 11143B) Bioavailability of Ibuprofen Oral Drops, 50 mg/1.25 mL

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Perrigo's Ibuprofen Oral Suspension Drops, 50 mg/1.25 mL and McNeil's Motrin® Oral Drops, 50 mg/1.25 mL, under fasting conditions.

Study Investigators and Facilities:

The study was conducted at PharmaKinetics, Baltimore, MD, between April 25 and May 3, 1997. The principal investigator was Clifford L. Ferguson, M.D.. Plasma samples were assayed by the same facility, under the supervision of [redacted] between May 8 and May 29, 1997.

Demographics:

Twenty-six normal, healthy male volunteers between 20-43 years of age, and within 15% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two-treatment, two-period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 129-198 lbs and 65-74 in, respectively. There were 16 black, 9 causasian and 1 other subjects.

Inclusion/exclusion criteria:

Subjects did not have any history of: asthma, nasal polyps, esophagitis, peptic or duodenal ulcer, organ-system (cardiovascular, neurological, hepatic, hematopoetic, renal, or gastrointestinal) disorders, ongoing infectious diseases, or alcohol or drug abuse; known allergy to ibuprofen, or sensitivity to aspirin or any other nonsteroidal anti-inflammatory drugs, such as ibuprofen, indomethacin, naproxen, or piroxicam.

Restrictions:

They were free of all prescription medications for 14 days, non-prescription medications for 7 days, alcohol at least 24 hours, and caffeine for at least 12 hours prior to each study period and allowed no concomitant medications during the study sessions. The subjects fasted for 10 hours overnight prior to and 5 hours after each drug administration. The washout duration between the two phases was 7 days. Duration of confinement was approximately 12 hours pre-dose to approximately 12 hours post-dose.

Treatments and Sampling:

The two treatments consisted of a single dose of 200 mg/5 mL of either the test product or reference product taken orally with 240 ml of water.

Test Product (Treatment A): Perrigo's Ibuprofen Oral Drops, 50 mg/1.25 mL, lot # 7P404V (Batch size of units of 2.5 ml, potency of 100.2%).

Reference product (Treatment B): McNeil's Motrin® Oral Drops, 50 mg/1.25 mL, lot # SJM157 (Potency of 98%).

Blood samples were collected at predose, 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours following drug administration. Blood samples were centrifuged and the plasma was separated and immediately stored at -20°C until analysis.

Assay Methodology:

The analytical method was developed by PharmaKinetics.

Assay Specificity:

The assay was specific for ibuprofen with no significant interferences seen at the retention time of the drug and internal standard in the chromatograms of the predose subject samples and blank plasma standards.

Linearity:

(Based on actual study standard curves)

The assay was linear in the range of 1.00 to 100.0 μg/mL.

Reproducibility:

(Based on actual study quality controls)

Interday CV's were: 3.18% at 2.50 μg/ml, 2.90% at 15.0 μg/ml and 1.98% at 75.0 μg/ml.

The control concentrations were approximately within the range of observed study subject concentrations.

Sensitivity:

(Based on actual study back-calculated standard data)

Sensitivity limit was 1.00 μg/ml (CV% = 3.51). Any level below this limit was reported as zero.

Prestudy assay validation data for LOQ as a quality control of 1.00 μg/mL: CV% = 12.5(n=20).

Accuracy:

(Based on actual study quality controls)

Percent recovery of control samples were: 100% at 2.50 μg/ml, 100% at 15.0 μg/ml and 99.8% at 75.0 μg/ml.

Stability:

Long-term stability of frozen samples was demonstrated along with the study samples using frozen control samples, 2.50 μg/mL and 75.0 μg/mL, which were prepared, stored at -20C, on April 24, 1997 and analyzed throughout the course of study sample analysis (May 8, 9, 20, 23, 24, 28 and 29, 1997). The mean results were compared with the theoretical values. The percent difference was less than 10% with no apparent trend of degradation. These data demonstrate the stability of ibuprofen in plasma for a 35 day period which covers the duration of both the clinical and analytical portions

of this study.

Short-term stability (24 hours at room temperature), freeze-thaw stability (3 cycles) and extracted sample stability (40 hours in autosampler) were evaluated and acceptable.

Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters. The 90% confidence intervals for AUC's, CMAX, lnAUC's and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test.

Results:

All twenty-six enrolled volunteers completed the clinical portion of the study. The statistical analysis was performed using 26 (balanced) data sets.

There was no significant difference (alpha=0.05) between treatments for all parameters analyzed. The results are summarized in the tables below:

Table I

Ibuprofen Comparative Pharmacokinetic Parameters

Dose=200 mg/ 5 mL; n=26

Parameters	Perrigo's Mean (CV%)	Motrin® Mean (CV%)	90% C.I.	Ratio T/R
AUC (0-T) μg.hr/ml	61.06*	64.97*	[0.99;1.07]	1.03
AUC (0-Inf) μg.hr/ml	64.97*	63.35*	[0.99;1.06]	1.03
CMAX(μg/ml)	19.78*	19.68*	[0.92;1.09]	1.01
TMAX (hrs)	0.87(60)	1.12(71)		
KEL (1/hrs)	0.365(13)	0.365(11)		
T1/2 (hrs)	1.93(14)	1.92(11)		

*Geometric Means

Table II
Comparative Mean Plasma Levels of Ibuprofen
Dose=200 mg/5 mL; n=26
μg/ml(CV%)

Hour	Perrigo's	Motrin®
0	0	0
0.17	5.878(70)	6.784(74)
0.33	12.48(41)	12.87(51)
0.5	16.84(38)	15.43(41)
0.67	18.22(32)	16.13(33)
0.83	18.36(27)	16.39(34)
1	17.23(25)	15.45(32)
1.33	15.45(21)	13.65(27)
1.67	13.74(21)	12.54(25)
2	12.98(21)	11.92(23)
2.5	10.88(23)	11.02(24)
3	9.247(26)	9.683(38)
4	6.678(29)	6.798(34)
5	4.980(36)	5.001(35)
6	3.301(41)	3.242(37)
8	1.535(54)	1.469(59)
10	0.388(172)	0.351(174)
12	0.0481(510)	0.0450(510)
AUC(0-T)$_{\mu g.hr/ml}$	62.94(26)	60.54(21)
AUC(0-Inf)$_{\mu g.hr/ml}$	66.82(25)	64.50(19)
CMAX	20.51(27)	20.07(19)

Adverse Effects:

One subject reported 1 adverse event (mild headache).

B. Non-Fasting Study: (Protocol No. 11144B) Bioavailability of Ibuprofen

Oral Drops, 50 mg/1.25 mL Effect of Food Study

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Perrigo's Ibuprofen Oral Suspension Drops, 50 mg/1.25 mL and McNeil's Motrin® Oral Drops, 50 mg/1.25 mL, under non-fasting conditions.

Study Investigators and Facilities:

The study was conducted at PharmaKinetics, Baltimore, MD, between April 24 and May 9, 1997. The principal investigator was Clifford L. Ferguson, M.D.. Plasma samples were assayed by the same facility, under the supervision o[illegible], between May 29 and June 9, 1997.

Demographics:

Eighteen normal, healthy male volunteers between 19-43 years of age, and within 15% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a three-treatment, three-period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 133-190 lbs and 65-75 in, respectively. There were 13 black and 5 causasian other subjects.

Inclusion/exclusion criteria: Same as in the Fasting Study above.

Restrictions: Same as in the Fasting Study except that for the non-fasting treatments (A & B) of the study, the drug was administered 35 minutes after subjects began the high-fat breakfast. The subjects were intructed to eat their entire breakfast in 30 minutes. The breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 1 serving of hash brown potatoes, 180 ml of orange juice and 240 ml of whole milk.

Treatments and Sampling:

The three treatments consisted of a single dose of 200 mg/5 mL of either the test product or reference product taken orally with 240 ml of water, under non-fasting or fasting conditions.

Test Product: Perrigo's Ibuprofen Oral Drops, 50 mg/1.25 mL, lot # 7P404V (Batch size of , . . , . . . units of 2.5 ml, potency of 100.2%), given immediately following a high-fat breakfast **(Treatment A)**, or given under fasting conditions **(Treatment C)**.

Reference product (Treatment B): McNeil's Motrin® Oral Drops, 50 mg/1.25 mL, lot # SJM157 (Potency of 98%), given immediately following a high-fat breakfast.

Blood samples were collected at predose, 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours following drug administration. Blood samples were centrifuged and the plasma was separated and immediately stored at -20°C until analysis.

Assay Methodology:

Assay Specificity:

The assay was specific for ibuprofen with no significant interferences seen at the retention time of the drug and internal standard in the chromatograms of the predose subject samples and blank plasma standards.

Linearity:

(Based on actual study standard curves)

The assay was linear in the range of 1.00 to 100.0 μg/mL.

Reproducibility:

(Based on actual study quality controls)

Interday CV's were: 2.66% at 2.50 μg/ml, 1.89% at 15.0 μg/ml and 1.87% at 75.0 μg/ml.

The control concentrations were approximately within the range of observed study subject concentrations.

Sensitivity:

(Based on actual study back-calculated standard data)

Sensitivity limit was 1.00 μg/ml (CV% = 3.35). Any level below this limit was reported as zero.

Prestudy assay validation data for LOQ as a quality control of 1.00 μg/mL: CV% = 12.5(n=20).

Accuracy:

(Based on actual study quality controls)

Percent recovery of control samples were: 100% at 2.50 μg/ml, 100% at 15.0 μg/ml and 100% at 75.0 μg/ml.

Stability:

Long-term stability of frozen samples was demonstrated along with the study samples using frozen control samples, 2.50 μg/mL and 75.0 μg/mL, which were prepared, stored at -20C, on April 24, 1997 and analyzed throughout the course of study sample analysis (May 29, June 2, 5, 6 and 9, 1997). The mean results were compared with the theoretical values. The percent

difference was less than 10% with no apparent trend of degradation. These data demonstrate the stability of ibuprofen in plasma for a 46 day period which covers the duration of both the clinical and analytical portions of this study.

Short-term stability (24 hours at room temperature), freeze-thaw stability (3 cycles) and extracted sample stability (40 hours in autosampler) were evaluated and acceptable.

Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters. The 90% confidence intervals for AUC's, CMAX, lnAUC's and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test.

Results:

Seventeen of 18 enrolled volunteers completed the clinical portion of the study. Subject #15 failed to return to the clinical facility after completing Period II. The statistical analysis was performed using 17 data sets.

There were significant differences (alpha=0.05) between treatments for all parameters analyzed (p=0.0002 or less). The results are summarized in the tables below:

Table III
Ibuprofen Comparative Pharmacokinetic Parameters
Dose=200 mg/ 5 mL; n=17
Non-Fasting Study

Parameters	Perrigo's(fed) Mean (CV%)	Motrin®(fed) Mean (CV%)	Perrigo's(fasted) Mean (CV%)	Ratio T (fed)/R (fed)
AUC (0-T) μg.hr/ml	60.37*	54.64*	63.64*	1.10
AUC (0-Inf) μg.hr/ml	63.85*	58.32*	67.82*	1.09
CMAX(μg/ml)	13.18*	11.59*	20.67*	1.14
TMAX (hrs)	3.39(30)	3.41(27)	0.872(69)	
KEL (1/hrs)	0.386(12)	0.407(14)	0.364(12)	
T1/2 (hrs)	1.82(12)	1.74(15)	1.93(13)	

*Geometric Means

Table IV

Comparative Mean Plasma Levels of Ibuprofen

Dose=200 mg/5 mL; n=17

μg/ml(CV%)

Non-Fasting Study

Hour	Perrigo's(fed)	Motrin®(fed)	Perrigo's(fasted)
0	0	0	0
0.17	0.368(196)	0.656(189)	6.732(56)
0.33	1.931(86)	2.719(80)	15.19(35)
0.5	3.285(68)	3.808(66)	19.08(26)
0.67	4.377(67)	4.611(54)	19.24(21)
0.83	5.391(58)	5.327(46)	18.39(18)
1	6.009(54)	5.685(41)	17.29(18)
1.33	6.965(39)	6.430(29)	15.56(17)
1.67	8.312(34)	7.075(26)	14.19(18)
2	9.199(33)	7.727(30)	12.93(21)
2.5	10.18(31)	8.696(31)	11.32(23)
3	10.62(27)	10.20(27)	9.420(24)
4	11.50(22)	10.47(16)	6.914(26)
5	8.600(21)	8.077(21)	5.148(28)
6	5.705(24)	5.217(23)	3.282(30)
8	2.589(31)	2.309(31)	1.483(57)
10	1.142(64)	0.824(92)	0.378(168)
12	0.197(223)	0.0776(412)	0.0735(412)
AUC(0-T)$_{\mu g.hr/ml}$	61.22(16)	55.31(16)	64.83(19)
AUC(0-Inf)$_{\mu g.hr/ml}$	64.71(16)	58.97(15)	68.90(18)
CMAX	13.36(16)	11.74(16)	20.99(18)

Adverse Effects:

There were 3 mild adverse events reported by 3 subjects: disturbed sleep pattern (Test treatment, fed), increased diastolic blood pressure (Test treatment, fed), and headache (Test treatment, fasted).

III. Dissolution Testing: USP method and specification

Drug (Generic Name): Ibuprofen Oral Suspension Drops Firm: L. Perrigo Company
Dose Strength: 50 mg/1.25 mL ANDA # 75-217
Submission Date: September 30, 1997

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:
USP XXIII Basket __ Paddle X RPM 50 Units Tested: 12
Medium: pH 7.2 0.05M Phosphate Buffer Volume: 900 ml
Reference Drug: (Manuf.) Motrin® Oral Drops (McNeil)
Assay Methodology: _____
USP Specification:

II. Results of In-Vitro Dissolution Testing:

Sampling Times (min.)	Test Product Lot # 7P404V Strength 50 mg/1.25 mL			Reference Product Lot # SJM157 Strength 50 mg/1.25 mL		
	Mean % Dissolved	Range	(CV)	Mean % Dissolved	Range	(CV)
15	101		(0.9%)	95		(1.6%)
30	101		(1.0%)	98		(2.0%)
45	101		(1.0%)	98		(1.9%)
60	101		(0.9%)	98		(2.2%)

IV. Comments:

1. The single-dose, fasting bioequivalence study and the single-dose, non-fasting bioequivalence study conducted by Perrigo on the test product, Ibuprofen Oral Drops, 50 mg/1.25 mL, comparing it with the reference product, Motrin® Oral Drops, 50 mg/1.25 mL, demonstrate that the test product is equivalent to the reference product in their rate and extent of absorption as measured by lnCMAX, lnAUC(0-T) and lnAUC(0-Infinity), under the fasting and non-fasting conditions.

2. The in vitro dissolution data for the test and reference products are acceptable.

V. Recommendations:

1. The single-dose, fasting bioequivalence study and the single-dose, non-fasting bioequivalence study conducted by Perrigo on the test product, Ibuprofen Oral

Drops, 40 mg/mL (or 50 mg/1.25 mL), lot # 7P404V, comparing it with the reference product, McNeil's Motrin® Oral Drops, 40 mg/mL (or 50 mg/1.25 mL), lot # SJM157, have been found **acceptable** by the Division of Bioequivalence. The study demonstrates that the test product, Perrigo's Ibuprofen Oral Drops, 40 mg/mL (or 50 mg/1.25 mL), is bioequivalent to the reference product, McNeil's Motrin® Oral Drops, 40 mg/mL (or 50 mg/1.25 mL), under fasting and non-fasting conditions.

2. The in-vitro dissolution testing conducted by Perrigo on its Ibuprofen Oral Drops, 40 mg/mL (or 50 mg/1.25 mL), has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of pH7.2 0.05M phosphate buffer at 37°C using USP XXIII apparatus II(paddle) at 50 rpm. The test product should meet the following tentative specifications:

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 2/27/98

Concur: Dale Conner Date: 2/27/98
Dale Conner, Pharm.D.
Director, Division of Bioequivalence